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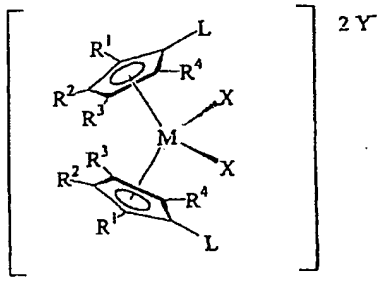
(54) Title: FUNCTIONALISED METALLOCENES AS ANTICANCER DRUGS



(1)

(57) Abstract: The invention provides metallocene compounds of formula (1) for use as medicaments in the treatment of cancer. Formula (1) wherein R^1, R^2, R^3 and R^4 represent a combination of H, alkyl, aryl or trimethylsilyl; L represents side chain substituents, at least one of which contains a group which enables the compound to become water-solubilised; X is halo, alkoxy, acetate or H_2O; Y is a counter-ion; and M is a metal. The invention also provides novel compounds of the formula (1) wherein at least one of the groups L comprises aquaternary tetraalkylammonium group. The compounds have been shown to have significantly greater activity in the treatment of cancer than the compounds known from the prior art.

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FUNCTIONALISED METALLOCENES AS ANTICANCER DRUGS

FIELD OF THE INVENTION

This invention relates to the use of functionalised metallocenes as anti-tumour reagents.

BACKGROUND OF THE INVENTION

A major problem with chemotherapy is the lack of selectivity of drugs for cancer cells. Consequently, the side effects of such treatment can be very unpleasant, and often worse than the symptoms of the actual disease. One of the best anticancer drugs known to those skilled in the art has been cisplatin, and the action and mechanism of this drug is now fairly well understood. However, the toxic side effects of cisplatin include nausea, vomiting, neuropathy, ototoxicity (tinnitus/hearing loss) and nephroxicity.[1] Although treatment with an alternative platinum based drug (carboplatin) lessens these side effects, this material has greater bone marrow toxicity.[2] Nevertheless, these compounds do find widespread medical usage in this field and the high specificity of cisplatin in treating testicular cancer suggests that it should be possible to synthesise other metal-based drugs to treat specific tumour types.

There has been a vigorous quest to locate effective new anti-cancer drugs, preferably having fewer side effects. Furthermore, new approaches are needed to tackle the problem of tumour resistance to cisplatin. For example, ovarian cancer patients initially respond well to the drug, but eventually develop resistance and succumb to the disease.[2] Amongst the candidates for antitumour reagents have been the early transition metal compounds, metallocene dichlorides $[(C_5H_5)_2MCl_2$, M = Ti, V, Nb, Mo, Re]. The antitumour activity of both titanocene (bis-cyclopentadienyl titanium) dichloride $[(C_5H_5)_2TiCl_2]$ or Cp_2TiCl_2 and vanadocene (bis-cyclopentadienyl vanadium) dichloride $[(C_5H_5)_2VCl_2]$ or Cp_2VCl_2 has been established against various animal and xenografted human tumours.[3,4]

Titanocene dichloride is one of the most effective anti-tumour agents of this type and is currently undergoing Phase II clinical trials.[5] On a toxicological and pharmacokinetic level, both Cp_2TiCl_2 and vanadocene dichlorides are interesting and effective antitumour drugs which differ from organic anti-tumour reagents and platinum cytostatic drugs by their pattern of toxicity and their pharmacokinetic behaviour.[3,6] *In vivo* research has shown xenografted tumours of the colon, head, breast, rectum, lung and stomach to be significantly sensitive to Cp_2TiCl_2 and generally to a greater extent than is found with cisplatin.[6]

Cp_2VCl_2 has been shown to have different activity than Cp_2TiCl_2; for example, with respect to their activity against different lung carcinomas.[7] For LX1, which is a histologically unclassified tumour which does not respond to most clinically used cytostatic drugs, Cp_2TiCl_2 displayed no significant anti-tumour activity, whereas Cp_2VCl_2 showed significant activity.[8] The consequence of this is that the nature of the active species is unknown and the administration of the compound as a drug can be difficult.

By their very nature, Cp_2TiCl_2 and Cp_2VCl_2 are flawed as drugs because of hydrolysis problems.[6,9] Hence, there is a requirement for the development of compounds which do not suffer from problems associated with aqueous instability, and it is an object of the present invention to provide such materials and to satisfy the requirements for new anti-cancer drugs. The present invention, therefore, seeks to provide a range of stable and active metallocenes as anticancer compounds.

It has been found that the stability, and thereby the solubility, of metallocene dichlorides in aqueous solutions is improved when the compound is ionic. Limited prior art exists in this area; however, of particular note is the ionic compound $[(C_5H_5)_2TiCl(NCCH_3)]^+ (FeCl_4)^-$, which was the subject of earlier studies relating to antitumour drugs.[3] It has also been established that ionic titanocenes of this type have been more effective against head and neck xenografts than both neutral titanocene and vanadocene dichlorides.[10]

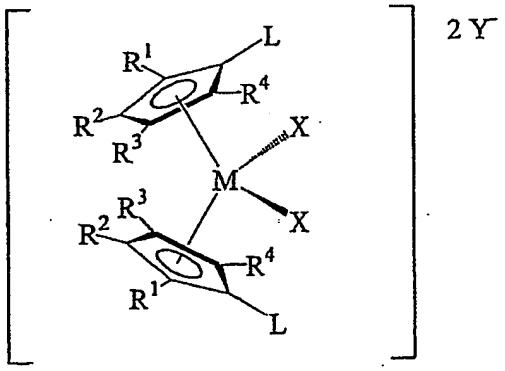
The present inventors, in the co-pending patent application published as WO 01/42260 have disclosed methods for the synthesis of metallocene halide salts having at least one cyclopentadiene group substituted by a basic group. However, that application contains no disclosure of the use of these materials for the treatment of cancer and, consequently, no data are provided for the success or otherwise of these materials in such treatments.

Most particularly, the present invention is concerned with various titanocene, vanadocene and molybdocene dichlorides, their synthesis and characterisation, and their use in the treatment of diseases, primarily cancer. The invention also involves an investigation of the efficiency of such compounds.

Thus, there are provided a number of water soluble metallocene halide salts, which have the potential to act as potent and effective anticancer agents. In addition, evidence is presented with regard to the increased stability and enhanced activity of these ionic metallocenes with respect to different sets of cancer cell lines.

STATEMENTS OF INVENTION

According to the first aspect of the present invention, there is provided a metallocene compound 1 for use as a medicament in the treatment of cancer.



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In 1: R^1, R^2, R^3 and R^4 represent a combination of H, alkyl, aryl or trimethylsilyl;
L represents side chain substituents, at least one of which contains a group which enables the compound to become water-solubilised;
X is halo, alkoxy, acetate or H_2O;
Y is a counter-ion; and
M is a metal.

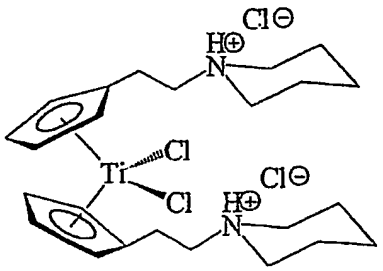
Preferably the metal is titanium, vanadium, niobium or molybdenum. Typical counter-ions include halide, acetate, tetrafluoroborate or hexafluorophosphate ions. The preferred titanocene, vanadocene niobiocene and molybdocene compounds are most preferably in the form of the dichloride salts. The compounds may be in the form of solvates or pro-drugs.

At least one cyclopentadienyl ring is functionalised by means of the group L such that the compound is water soluble. Preferably the at least one cyclopentadienyl ring is functionalised by a group L that carries a pendant Lewis base which confers aqueous solubility, such as an amino-functionalised side chain which can be quaternised.

Typically, in order to funtionalise the cyclopentadienyl ring, the group L comprises an alkyl group with a terminal Lewis base and preferably L has the formula

$$-(CH_2)_nZ$$

wherein n is an integer from 1 to 20 and Z comprises an amino group, for instance a secondary amino group, a particularly favoured example being a $-(CH_2)_2N(CH_2)_5$ group, which may be quaternised to provide compounds such as those of formula 2 or 3. These compounds may comprise trialkyl ammonium halides, such as the compound of formula 2 or, most advantageously, novel tetraalkylammonium compounds including the compound of formula 3.



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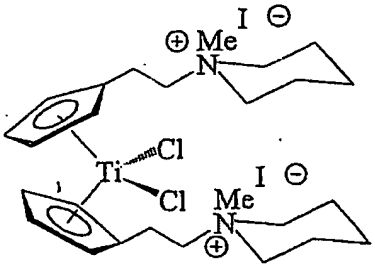

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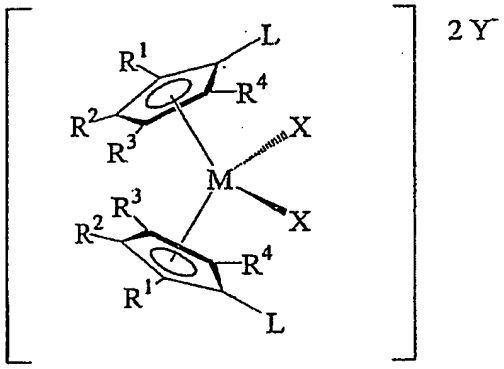
Thus, according to a further aspect of the present invention, there is provided a metallocene compound of formula **1**



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wherein R^1, R^2, R^3 and R^4 represent a combination of H, alkyl, aryl or trimethylsilyl;

L represents side chain substituents, at least one of which contains a quaternary tetraalkylammonium group;

X is halo, alkoxy, acetate or H_2O;

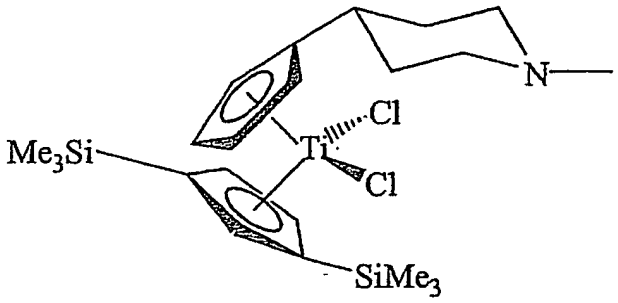
Y is a counter-ion; and

M is a metal.

In any event, according to either aspect of the invention, at least one of the L groups comprises a functionalised substituent capable of enabling the compound to become water-solubilised, and both groups may comprise such substituents. However, on the occasions when only one of the L groups comprises such a functionalised substituent,

then the L group on the other cyclopentadienyl ring may comprise any substituent not associated with conferring aqueous solubility on the molecule, typical examples being alkyl, aryl, aralkyl or, preferably, trialkylsilyl groups, for example, trimethylsilyl groups; alternatively, in such cases, L may be hydrogen.

Particular examples of compounds wherein only one of the L groups comprises a functionalised substituent include those of formulae **4**, **5**, **6** and **7**.



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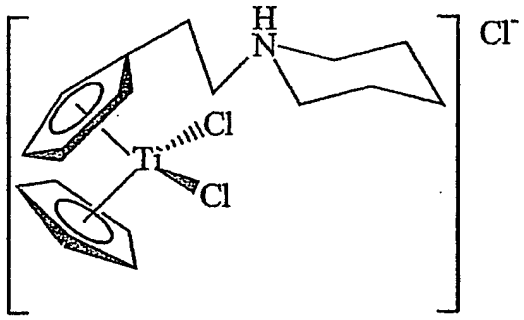

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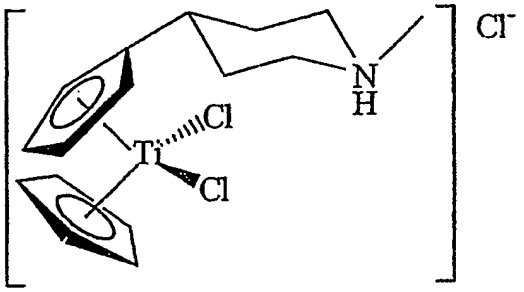

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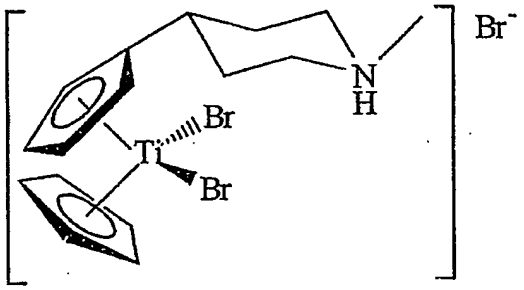

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Specifically, the present invention relates to a series of compounds having an ionic feature which is contained within the ligand. This ionic character enables the compounds to overcome the problems of poor water solubility and instability to hydrolysis which are associated with the compounds of the prior art. Thus, the compounds are found to act as potent anti-tumour reagents.

The invention provides a method of treating and/or preventing cancer, which encompasses the administration of a therapeutically effective amount of the compounds **1** to the patient.

Administration of the compounds of invention comprises of a number of routes including orally, parenterally, topically, nasally or via slow releasing microcarriers.

Suitable excipients include, saline, sterile water, creams, ointments, solutions, gels, pastes, emulsions, lotions, oils, solid carriers and aerosols.

The specific amount of compound required will depend on a number of factors, such as the biological activity of the compound used and the age, body and sex of the subject. The subject may be a human or mammalian animal.

The compounds and compositions of the invention can be administered alone or in combination with other compounds. The other compounds may have a biological activity, which complements the activity of the compounds of the invention, e.g., by enhancing its effect in killing tumours or by reducing side effects associated with the compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Preferably the metal is a group IV metal, more preferably, titanium, an example being $[Cp(CH_2)_2NH(CH_2)_5]_2TiCl_2.2HCl$ **2**, which was tested against a number of cell lines, as detailed in Tables 1 and 2.[11] Of particular significance is that **2** is much more active when compared to Cp_2TiCl_2; **2** is almost a factor of 10 times more potent than Cp_2TiCl_2.[5] Indeed, the compounds of the present invention, which show much greater stability in aqueous media than the compounds of the prior art, are generally found to be around 10 times more potent towards certain cancer cell lines than is the case with cisplatin.

In order to determine whether these types of complexes overcome platinum resistance *in vitro*, the anti-proliferative effects of **2** on cisplatin-resistant A2870 were examined (see Table 3). As ovarian tumours often develop resistance to platinum compounds, these lines present a good model for screening. After 144 hours, cisplatin appears to be 3 times more resistant than **2**. The dramatic decrease in resistance factor suggests that these functionalised titanocene dichloride compounds

confer a potent anti-proliferative effect on platinum-resistant ovarian tumour cell lines.

Furthermore, changing the group attached to the amino functionality has a dramatic effect on the efficacy of the drugs for A2780 cell line, but not for the cisplatin resistant cell line of A2870-cis, as indicated in Table 4, which includes comparative data for the compounds of formulae **2** and **3**. A particular advantage of the compounds of the present invention is their enhanced activity towards cisplatin-resistant cell lines; it is found that the activity of these compounds remains constant whilst the effects of cisplatin diminish.

CELL LINE	*DRUG*	*IC50 (μM)*	*DIFFERENTIAL* (μM)
MCF-7	Cisplatin	9	-
	2	62	6.9
LoVo	Cisplatin	0.37	-
	2	62	167.6
LS 174T	Cisplatin	0.50	-
	2	36	72
A2780	Cisplatin	0.82	-
	2	31	37.8
A2780-*cis*	Cisplatin	2.1	-
	2	28	13.3
A2780 (24 hour)	Cisplatin	1	-
	2	168	168
A2780-*cis* (24 hour)	Cisplatin	5.4	-
	2	154	28.5

Table 1. The sensitivity of cell lines to Cisplatin and Ti Compounds

CELL LINE	CISPLATIN	2
LoVo	1	1
MCF-7	24.3	1
LS-174T	1.35	0.58
A2780	2.2	0.5
A2780*cis*	5.7	0.45

Table 2. The relative sensitivity of cell lines to Cisplatin and Ti Compounds

CELL LINE	EXPOSURE TIME (hr)	DRUG	
		CISPLATIN	2
A2780	144	1	1
A2780*cis*	144	2.56	0.90
A2780	24	1.22	5.42
A2780*cis*	24	6.59	4.97

Table 3. The relative sensitivity of A2780 and A2780cis cell lines to Cisplatin and Ti Compounds

CELL LINE	*DRUG*	*IC50(μM)(7 days)*
A2780	2	99.1
	3	765.6
A2780cis	2	4.3
	3	5.2

Table 4. The relative sensitivity of A2780 and A2780cis cell lines to Ti-2 and Ti-4 Compounds

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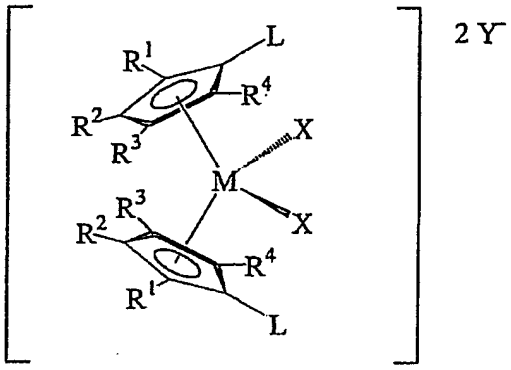
CLAIMS

1. A metallocene compound of formula 1 for use as a medicament in the treatment of cancer.



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wherein R^1, R^2, R^3 and R^4 represent a combination of H, alkyl, aryl or trimethylsilyl;

L represents side chain substituents, at least one of which contains a group which enables the compound to become water-solubilised;

X is halo, alkoxy, acetate or H_2O;

Y is a counter-ion; and

M is a metal.

2. A metallocene compound as claimed in claim 1 wherein the metal M is titanium, vanadium, niobium or molybdenum.

3. A metallocene compound as claimed in claim 1 or 2 wherein the counter-ion Y is a halide, acetate, tetrafluoroborate or hexafluorophosphate ion.

4. A metallocene compound as claimed in claim 1, 2 or 3 which is in the form of the dichloride salt.

5. A metallocene compound as claimed in any one of claims 1 to 4 which is in the form of a solvate or a pro-drug.

6. A metallocene compound as claimed in any preceding claim wherein both groups L are functionalised to enable the compound to become water-solubilised.

7. A metallocene compound as claimed in any preceding claim wherein only one group L is functionalised to enable the compound to become water-solubilised.

8. A metallocene compound as claimed in any preceding claim wherein L comprises a group which carries a pendant Lewis base.

9. A metallocene compound as claimed in claim 8 wherein the Lewis base is provided by an amino group.

10. A metallocene compound as claimed in claim 9 wherein the amino group is a secondary amino group.

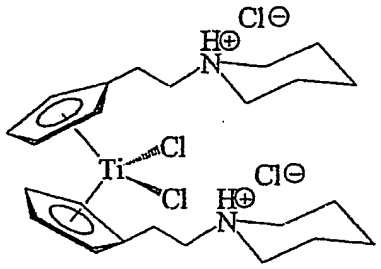
11. A metallocene compound as claimed in claim 10 wherein the secondary amino group comprises a $-(CH_2)_2N(CH_2)_5$ group.

12. A metallocene compound as claimed in claim 9 wherein the group L has the formula

$$-(CH_2)_nZ$$

wherein n is an integer from 1 to 20 and Z comprises an amino group.

13. A metallocene compound as claimed in claim 1 which has the formula 2:



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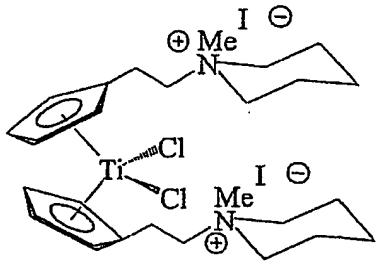
14. A metallocene compound as claimed in claim 1 which has the formula 3:



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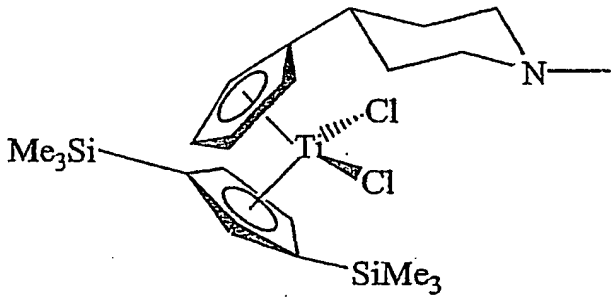
15. A metallocene compound as claimed in claim 1 which has the formula 4:



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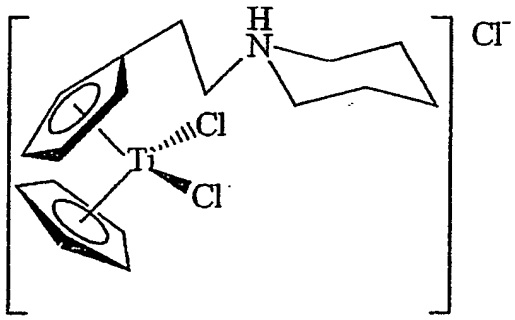
16. A metallocene compound as claimed in claim 1 which has the formula 5:



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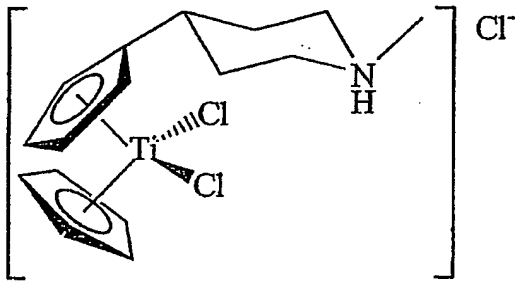
17. A metallocene compound as claimed in claim 1 which has the formula 6:



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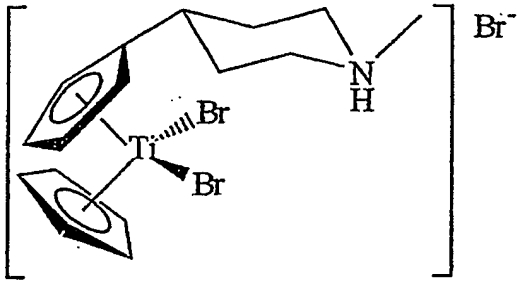
18. A metallocene compound as claimed in claim 1 which has the formula 7:



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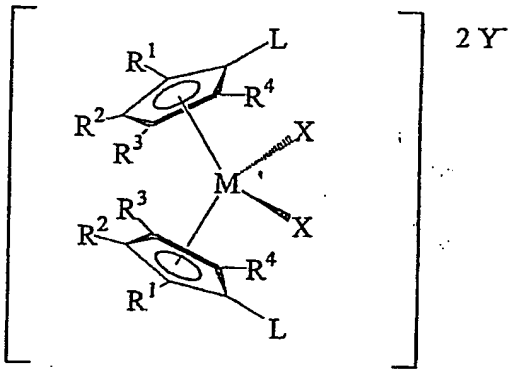
19. A metallocene compound of formula 1



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wherein R^1, R^2, R^3 and R^4 represent a combination of H, alkyl, aryl or trimethylsilyl;

L represents side chain substituents, at least one of which contains a quaternary tetraalkylammonium group;

X is halo, alkoxy, acetate or H_2O;

Y is a counter-ion; and

M is a metal.

20. A metallocene compound as claimed in claim 19 wherein the metal M is titanium, vanadium, niobium or molybdenum.

21. A metallocene compound as claimed in claim 19 or 20 wherein the counter-ion Y is a halide, acetate, tetrafluoroborate or hexafluorophosphate ion.

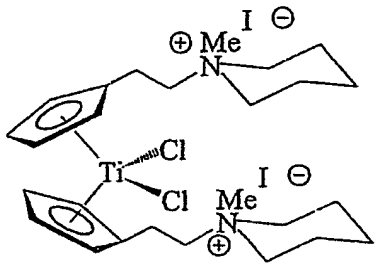
22. A metallocene compound as claimed in claim 19, 20 or 21 which is in the form of the dichloride salt.

23. A metallocene compound as claimed in any one of claims 19 to 22 which is in the form of a solvate or a pro-drug.

24. A metallocene compound as claimed in any one of claims 19 to 23 wherein both groups L comprise a quaternary tetraalkylammonium group.

25. A metallocene compound as claimed in any preceding claim wherein only one group L comprises quaternary tetraalkylammonium group.

26. A metallocene compound as claimed in claim 19 which has the formula 3:



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27. A metallocene compound as claimed in any preceding claim for administration to a patient orally, parenterally, topically, nasally or via slow releasing microcarriers.

28. A metallocene compound as claimed in any preceding claim wherein excipients comprise saline, sterile water, creams, ointments, solutions, gels, pastes, emulsions, lotions, oils, solid carriers or aerosols.

29. A metallocene compound as claimed in any preceding claim for administration alone or in combination with at least one other compound.

30. A metallocene compound as claimed in claim 29 wherein said at least one other compound has biological activity.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 03/02886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 42260 A (MCGOWAN PATRICK COLUMBA ;UNIV LEEDS (GB); MCGOWAN MARGARET DYMPHNA) 14 June 2001 (2001-06-14) cited in the application page 1, line 19 - line 27 page 6, line 18 - line 24	1-30
Y	TONEY, J.H.; MARKS, T.J: J. AM. CHEM. SOM., vol. 107, 1985, pages 947-953, XP002257006 cited in the application the whole document	1-30
Y	WO 94 04142 A (KEINAN EHUD) 3 March 1994 (1994-03-03) the whole document	1-30

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2003	29/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Zellner, A

Form PCT/ISA/210 (second sheet) (July 1992)

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International Application No
PCT/EP 03/02886

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 202 673 A (KOPF HARTMUT ;KOPF MAIER PETRA (DE)) 26 November 1986 (1986-11-26) the whole document	1-30
Y	US 5 863 911 A (JAOUEN GERARD ET AL) 26 January 1999 (1999-01-26) column 3, line 35 - line 56	1-30
Y	US 4 851 430 A (KOEPF-MAIER PETRA ET AL) 25 July 1989 (1989-07-25) the whole document	1-30
Y	JUTZI P ET AL: "DER (N,N-DIMETHYLAMINOETHYL)CYCLOPENTADIENYL-LIGAND IN DER KOMPLEXCHEMIE VON TITAN UND ZIRKON" JOURNAL OF ORGANOMETALLIC CHEMISTRY, ELSEVIER-SEQUOIA S.A. LAUSANNE, CH, vol. 486, no. 1/2, 25 January 1995 (1995-01-25), pages 287-289, XP000615611 ISSN: 0022-328X the whole document	1-30
Y	JUTZI, P.; ET AL.: ORGANOMETALLICS, vol. 15, 1996, pages 4153-4161, XP002257007 the whole document	1-30
A	DE 41 35 292 A (USUI KOKUSAI SANGYO KK) 14 May 1992 (1992-05-14) the whole document	1-30

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ational application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-8, 27-30 (all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8, 27-30 (all part)

Present claims 1-8, 27-30 relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. In particular the use of the expression "which enables the compound to become water-solubilised" does not permit to clearly define the claimed subject-matter. The claim merely recites the technical problem to be solved. Consequently, the search has been carried out for those parts of the application which do appear to be clear and supported by the description, namely those compounds of formula 1 wherein L comprises an amino group (claim 9).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inte al Application No
PC.,_J 03/02886

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